DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No.: 98-0286

November 2, 1998

Sally R. Gould
Immunex Corporation
51 University Street
Seattle, WA 98101

Dear Ms. Gould:

Your biologics license application for Etanercept is approved effective this date. Immunex Corporation, Seattle, Washington, is hereby authorized to introduce or deliver for introduction into interstate commerce Etanercept under Department of Health and Human Services U.S. License No. 1132.

Etanercept is indicated for reduction in signs and symptoms of moderately to severely active rheumatoid arthritis in patients who have had an inadequate response to one or more disease-modifying antirheumatic drugs (DMARDS). Etanercept can be used in combination with methotrexate in patients who do not respond adequately to methotrexate alone.

Under this authorization you are approved to manufacture Etanercept under contract at ——— Drug product will be filled and labeled at ——— Labeled drug product vials will be shipped to a contract packaging facility, ——— and packaged with pre-filled syringes containing Bacteriostatic Water for Injection, USP (BWFI). Packaged Etanercept will be distributed by Immunex's contract distributor, ——— In accordance with approved labeling, your product will bear the tradename Enbrel and will be marketed in a dose tray containing one 25 mg single use vial, one prefilled diluent syringe, one plunger and two alcohol swabs.

You are not currently required to submit samples of future lots of Etanercept to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 12 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the final formulated product. The dating period for the diluent, BWFI, shall be 36 months. The expiration date for the packaged product, Enbrel plus diluent, shall be dependent on the shortest expiration date of either component. The bulk drug substance may be stored in portable stainless steel storage vessels for up to 12 months at -20°C or for up to 3 months at 2-8°C. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots. The stability protocol in your license application is considered approved for the purpose of extending the expiration dating period of your drug substance and drug product as specified in 21 CFR 601.12.

Any changes in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

We acknowledge your written commitments of October 22, 1998, October 27, 1998, and October 29, 1998 which include the following:

1. To develop quantitative lot release assays and set specifications for [redacted] by Q3 1999; to continue to monitor levels of these impurities using an interim modified SDS-PAGE method and to report all lots that exceed a reasonable interim action limit to CBER; and to submit a report of the results of the [redacted] SDS-PAGE survey for impurities upon completion.

2. To validate the [redacted] method as a lot release test for bulk drug substance (BDS) and drug product (DP) by Q4 1998 and to set specifications after manufacture of 20 lots at [redacted] scale. To evaluate the [redacted] method as a stability indicating assay and to incorporate it into the stability protocol if warranted.

3. To implement near term (Q4 1999) and long term improvements in the manufacturing process to minimize in-process impurities and product degradants.

4. To design and validate an improved ELISA for detecting anti-Enbrel antibodies in patient sera collected during phase 4 clinical studies.

5. To adjust lot release specifications for BDS and DP following manufacture of 20 lots at the [redacted] scale.

6. To establish alert and action limits for bioburden, endotoxin and in-process parameters for key intermediates (bioburden sampling to be performed before in-line sterile filtration steps) by Q4 1998.

7. To complete validation of the ——— ELISA by Q4 1998.

8. To repeat the harvest pool storage validation study on three BDS lots after validating the ——— ELISA; to include bioburden and LAL as test parameters for harvest storage validation; to include an analysis for matrix effects of harvest media on the ——— ELISA; and to set predetermined acceptance specifications for ——— concentration using the validated ——— ELISA before and after ——— ——— by Q1 1999.

9. To repeat the unfiltered media hold validation study by Q4 1998; and to reduce the bioburden acceptance specification of ——— CFU/ml for storage of unfiltered media.

10. To revalidate the cross reactivity of ——— in the process related impurities (PRI) assay at the same concentration ——— used to test ——— by Q1 1999.

11. To set alert and action limits on critical parameters associated with the ——— virus filtration unit by Q1 1999.

12. To retain ——— representative on site at ——— for at least one year past the date of FDA approval; and to evaluate the need for Immunex onsite oversight of manufacturing operations annually.

13. To evaluate the ability of porcine parvovirus (PPV) to directly infect the CHO — cell line.

14. To submit monthly production lot summaries for Enbrel during the first year following FDA approval, and to discuss the need for continued submissions at the end of the first year.

15. To evaluate long-term safety of Enbrel in Protocol 16.0018 until patients have been treated with Enbrel for 3 years; and once these data are analyzed to discuss with FDA whether the study should be continued or closed.

16. To initiate a study in Q4 1998 to evaluate antibody response to pneumococcal vaccine in order to assess functionality of B lymphocytes in Enbrel treated patients.

17. To initiate a study in Q2 1999 to evaluate safety of a higher dose of Enbrel in a randomized double-blind study of 25 mg Enbrel (subcutaneously twice weekly) versus the higher Enbrel dose.

18. To initiate an additional pharmacokinetic study by the end of Q2 1999 to provide further single-dose and multiple-dose pharmacokinetic data.

19. To initiate a study by the end of Q2 1999 to evaluate the safety of Enbrel in combination with other commonly used DMARDs.

20. We also acknowledge ——— letters of June 15, 1998, October 13, 1998, and October 26, 1998 addressing the Agency's observations noted during the April 27, 1998 - May 8, 1998 and October 5-8, 1998 inspections at ——— and their commitments to implement corrective actions within specified timelines.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 or Form 2253 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567 or Form 2253.

All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research